In the Claims

Please cancel claims 27, 28 and 50-58 without prejudice to applicants' right to pursue patent protection for the cancelled subject matter in a later filed divisional or continuation application.

The above amendment adds no new matter to this application.

Remarks

Claims 1-68 are pending in the present application[1]. Favorable reconsideration of the claims is respectfully requested. Applicants have hereinabove-cancelled claims 27, 28 and 50-58 without prejudice to applicants' right to pursue patent protection for the cancelled subject matter in a later filed divisional or continuation application. Applicants respectfully request that the Examiner enter this Amendment. Upon entry of this Amendment the pending claims are 1-26, 29-49 and 59-68.

Applicants elected in their October 21, 2002 response to a Restriction Requirement to prosecute claims 1-49 of Group I in this application. Accordingly, claims 50-68 are now drawn to non-elected subject matter. Applicants herein have cancelled non-elected claims 50-58 of the subject application. Applicants have not cancelled non-elected method of use claims 59-68 since they are drawn to subject matter which is eligible for rejoinder pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86). Also see M.P.E.P. § 821.04 "Rejoinder". Claims directed to process for making and/or using the product, which depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance. Id. In order to expedite prosecution M.P.E.P. § 821.04 recommends that applicants present rejoinder claims, preferably as dependent claims, in the application at an early stage of prosecution. Id. Applicants respectfully submit that rejoinder is applicable for the method of use claims 59-68. Applicants originally elected to have claims 1-49 examined first. Method of use claims 59-68 are written in dependent form as suggested in M.P.E.P. §821.04 for rejoinder to the product claims. Applicants respectfully request that

[1] Applicants note that the Examiner in the Office Action Summary states that claims 1-68 are pending in the subject application. However, on page 2 in the Detailed Remarks the Examiner states that claims 1-66 are pending in the application. Applicants believe this to be an inadvertent error. As noted above claims 1-68 are currently pending in the subject application.

claims 59-68 be rejoined with the pending product claims and fully examined for patentability under 37 C.F.R. § 1.104.

Applicants wish to thank the Examiner for his acknowledgement of their claim for domestic priority under 35 U.S.C. §119(e) for the subject application.

I. Enablement Rejection Under 35 U.S.C. §112, first paragraph for Claims 1-12, 15-26 and 49

Claims 1-12, 15-26 and 49 were rejected by the Examiner under 35 U.S.C. §112, first paragraph, as allegedly not been enabled for the preparation and use of compounds wherein R^2 is a functional group other than indole or quinoline. The Examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is mostly nearly connected, to practice the claimed invention commensurate in scope with the claims. Applicants respectfully traverse this position for the following reasons.

The Examiner in support of his position states on page 2 of the Office Action that applicants' claimed invention embrace a diversity of chemical and physically distinct compounds, wherein R^2 can be a 5-13 membered unsubstituted or substituted, fused or unfused hetereocyclic group containing one more heteroatoms. The Examiner provides no evidence nor cites any facts to support his position that the specification of the claimed invention does not enable the full scope of the claimed invention. If the Examiner is basing his rejection upon his own prior knowledge applicants respectfully request the Examiner identify the source of his underlying rejection and not based it upon conclusory statements.

Applicants respectfully submit that claims 1-12, 15-26 and 49 are enabled by the specification of the subject application. The Court of Customs and Patent Appeals (C.C.P.A.), which has now been superseded by the Court of Appeals for the Federal Circuit, stated in In re Borkowski, 164 U.S.P.Q. 642 (C.C.P.A. 1970) that "[t]here is no magical relationship between the number of representative examples and the breath of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode' contemplated.'" Id. at 646. Applicants respectfully submit that they have provided an enabling disclosure for the full scope of claims 1-12, 15-26 and 49. The applicants have, therefore, complied with the statutory requirements of §112.

The C.C.P.A. has stated that the specification need not contain a working example of every embodiment of the invention "if the invention is otherwise disclosed in a manner that one skilled in the art would be able to practice it." Id. at 645. Also see U.S. v. Telectronics, Inc., 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Applicants respectfully submit that the specification of this case contains support sufficient to enable one of ordinary skill in the art to practice the inventions of each of the claims 1-12, 15-26 and 49.

In this regard, applicants respectfully direct the Examiner's attention to the detailed synthetic schemes that have been provided. Applicants have provided detailed synthetic schemes on pages 19 through 21 of the subject application that teach one of ordinary skill in the art how to make the claimed compounds of the present invention. Moreover, applicants have provided a detailed written description on pages 22-24 of the reaction steps employed in the aforementioned synthetic schemes. The specification also sets forth in detail over 74 representative examples of compounds of the claimed invention that were prepared using the disclosed synthetic schemes. Furthermore, applicants have provided a number of references to patent publications for preparing the compounds of the present invention (see, page 22, line 9 through line 12).

Applicants respectfully submit that one of ordinary skill in the art would be capable of making applicants' claimed compounds different from those specifically described.

> "*It is manifestly impractical for an applicant who discloses a generic invention to give an example of every such species.* It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Kamal, 398 F.2d 867, 158 U.S.P.Q. 320, 323 (C.C.P.A. 1968), quoting In re Grimme, 274 F.2d 949, 124 U.S.P.Q. 499, 501 (C.C.P.A. 1960) (emphasis added). An applicant need not provide a specific example of everything embraced by a broad claim. In re Anderson, 471 F.2d 1237, 176 U.S.P.Q. 331 (C.C.P.A. 1973).

Applicants respectfully submit that they have taught those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The law does not require applicants to disclose an example of every claimed compound. The specification of

the subject application provides sufficient detail for one of ordinary skill in the art to prepare the claimed invention. Furthermore, preparation of additional compounds is a matter of routine experimentation given that the high level of skill and knowledge in the art.

Applicants reiterate the fact that they have provided a specification that contains detailed synthetic schemes providing guidance on the preparation of the claimed compounds and also provided a large number of working examples. Furthermore, applicants have identified a large amount of reference material for the preparation of the compounds of the present invention on page 17 of the subject application. Accordingly, applicants' disclosure coupled with the high level of skill in the well-developed organic synthesis art is sufficient to enable one of ordinary skill in the art to practice the claimed invention.

The Examiner has not supported his position that the disclosure of the subject application does not enable those of ordinary skill in the art to practice the invention. The Examiner merely makes a conclusory statement the applicants' definition of compounds wherein R^2 is a 5-13 membered hetereocyclic is not enabled. The Examiner fails to provide any support for why he believes on of ordinary skill in the art is not enabled to practice the invention based upon the disclosure.

It is unreasonable for the Examiner to expect applicants to provide examples of each and every 5-13 membered heterocyclic. A patent application is not a production document. It is not necessary for applicants to teach what is well-known in the art. In re Bruchner, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991). In fact, the Federal Circuit has stated that a patent preferably *omits* such information. Id. In the chemical arts there is an extensive body of knowledge in the prior art from which one of ordinary skill in the art can draw on. One well-known term of art is "5-13 membered heterocyclic". Furthermore, applications have provide a detailed definition of "5-13 membered heterocyclic" on page 16, lines 15 to 36 of the application. Nothing further is required. The Examiner has not articulated why he believes that one of ordinary skill in the art could not make compounds having a 5-13 membered heterocyclic substituent different from those shown in the Examples of the subject application. It is not necessary for applicants to teach what is already well-known in the art. Applicants' patent application is not required to be a production specification.

The test of enablement is not whether any experimentation is necessary, but whether, it experimentation is necessary, it is undue. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A.

1976). It is a matter of routine experimentation for one of ordinary skill in the art to make compounds of the claimed invention with heterocyclics different from those disclosed in the specification. Accordingly, applicants respectfully submit that one of ordinary skill in the art can practice the claimed invention without an undue amount of experimentation.

On page 3 of the Action the Examiner asserts states that "[t]he testing data is limited to a number of compounds not considered to be representative of all compounds encompassed by the claims" and that "one skilled in the art could not reasonably extrapolate the activities of the claimed compounds to other structurally divergent compounds embraced by claims which have not been tested." For the reasons that follow, applicants respectfully disagree with the Examiner's position.

Applicants respectfully submit that the specification of this case contains support sufficient to enable those skilled in the art to practice the inventions of each of the claims. Applicants' specification adequately discloses to one skilled in the relevant art how to make and use the claimed invention without undue experimentation. The pharmaceutically active compounds employed in these claims are described on pages 2-8 of the specification, and methods by which such compounds can be prepared are described in detail on pages 19 to 24 of the specification. All the descriptions in the specification that are referred to above are written in clear and concise language using terms that are familiar to those skilled in the art.

Moreover, the specification sets forth in detail, on pages 1-2, that the compounds of the present application inhibit the receptor tyrosine kinase and that such activity has been correlated with the treatment of the various disorders recited in claims 59-68. Further, on pages 26 through page 29 of the specification sets forth *in vitro* and *in vivo* tests which can be followed to assess the activity of any compound falling within the scope of the present application. Moreover, on pages 29-30, the specification describes how the methods of claims 59-68 can be carried out by those skilled in the art. It specifies, on these pages, appropriate dosages and methods of administration. This description includes the various modes by which the compounds employed in the claimed methods can be administered to mammals, the pharmaceutically acceptable forms in which they can be administered and appropriate dosages for their administration. The foregoing information is sufficient to enable one skilled in the art to practice the inventions of each of the pending method claims and thus complies with the requirements of 35 U.S.C. §112, first paragraph.

In the decision of In re Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), the court stated,

> A specification disclosure that contains a teaching of the manner and process of making and using the invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. . . . In any event, it is incumbent upon the patent office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

The Examiner's conclusory statement that the claimed invention is not enabled is not sufficient without underlying reasons or support for such an assertion. Applicants respectfully submit that the Examiner has not proffered *any* evidence that would cause one skilled in the art to doubt the objective truth of the enabling support set forth in the present specification. The Examiner has not explained *why* he doubts the accuracy of applicants asserted utility for the claimed compounds. The burden is on the Examiner to come forth with evidence to establish a *prima facie* case of non-enablement. Ex parte Hitzeman, 9 U.S.P.Q. 2d 1821, 1822 (Pat. Off. Bd. App. 1987); In re Armbruster, 185 U.S.P.Q. 152, 153 (C.C.P.A. 1975); In re Marzocchi, 169 U.S.P.Q. at 370. Applicants respectfully submit that the patent office has not met its burden of proof in calling into question the enablement of applicants' disclosure. Accordingly, a *prima facie* case of non-enablement for the claimed invention has not been established.

Furthermore, applicants respectfully submit that they are not required under the first paragraph of 35 U.S.C. §112 to provide chemical or biological data or to otherwise substantiate that their claimed compounds and compositions are useful in treating the various disorders and

conditions named in the rejected claims. This paragraph requires only that they provide a description of each claimed invention, in clear and concise terms, that is sufficient to enable those of skill in the art to practice each such invention, including what they contemplate to be the best mode of practicing each such invention. As explained in detail above, applicants have satisfied this requirement.

Applicants respectfully submit that one of skill in the art would not need data to practice the inventions of claims 59-68. The specification teaches that all the compounds employed in the pharmaceutical compositions and methods of these claims are inhibitors of the receptor tyrosine kinase and that they are useful in treating the various named disorders and conditions. The Examiner has not proffered any evidence to show that those skilled in the art would doubt the objective truth of these statements. Therefore, such statements must, as indicated above, be accepted as true.

Applicants also respectfully submit that experimental examples are not required to support the complete scope of a claim. Working examples are not a necessary part of a patent application. Neither the patent laws nor the U.S.P.T.O. Rules of Practice require that a patent application contain any working examples of a claimed invention. As stated in In re Goffe, 191 U.S.P.Q. 429, 431 (C.C.P.A. 1976), it is contrary to the original intent of the Patent Laws in this country to require an applicant to limit the claims to materials disclosed in the examples. ("To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for 'preferred' materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.").

The number and variety of examples are irrelevant if the disclosure of the patent application is enabling and sets forth the best mode contemplated. In re Borkowski, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970).

Applicants have submitted an enabling disclosure, including what they believe to be the best mode for making all the compounds claimed in this application. They have therefore complied with the statutory requirements of §112.

The Examiner's obligation is clearly to ground his reasoning in factual evidence, see M.P.E.P. §2164.04, which states:

> As stated by the court, "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explains why it doubts the truth or accuracy of any statement in a supporting disclosure and *to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.* Otherwise there would be no need for the applicant to go to the trouble and expense of supporting her presumptively accurate disclosure."... This can be done by making specific findings of facts, supported by the evidence, and then drawing conclusions based on these findings of fact (emphasis added).

The Examiner has failed to provide any evidence or logical reasoning to doubt the truth or accuracy of applicants' statements in the specification of the subject application. The Examiner again has merely provided a conclusion without any underlying support for his position. The Examiner as noted above in M.P.E.P. §2164.04 is required to do more. The Examiner has not done so in the examination of the present application.

Applicants also wish to note that the Federal Circuit in In re Brana, 34 USPQ2d 1437 (Fed. Cir. 1995) addressed an appeal involving a rejection of claims under 35 U.S.C. §112, first paragraph. The claims were rejected on the basis that certain tests provided in the patent application allegedly did not provide a reasonable basis for concluding that the claimed compounds possessed antitumor activity. Since the rejection focused on whether the claimed compounds possessed a practical utility, the Court noted that the rejection could also have been brought under 35 U.S.C. §101. After ruling that the PTO did not meet its "initial burden of challenging a presumptively correct assertion of utility in the disclosure," the Court stated "we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness." Id. at 1441. The Court went on to make the following compelling point, which is relevant to the present application, "The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. [cite omitted] Modern science has previously identified numerous successful chemotherapeutic agents." Id. Given this persuasive legal precedent, applicants respectfully submit that the claims and specification of the present application meet the enablement requirement of §112, first paragraph. Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 1-12, 15-26 and 49 under §112, first paragraph.

II. Enablement Rejection Under 35 U.S.C. §112, first paragraph for Claims 1 and 15

On page 4 of the Action the Examiner also rejected claims 1 and 15 under §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as not to enable one skilled in the are to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner rejected the use of the term "prodrug" in claims 1 and 15 as not been enabled. The Examiner asserts that "no guidance as how the compounds are made more active in vivo" and that "the choice of prodrug will vary from one drug to drug". The Examiner concludes that more than routine experimentation would be required to determine which prodrug will be suitable for the instant invention. Applicants respectfully disagree with the Examiner's position and the Examiner's flawed logic in rendering a §112, first paragraph enablement rejection for the following reasons.

Firstly, applicants respectfully submit that the term "prodrug" is well-known and familiar term to those of ordinary skill for the instant invention. Applicants have also provided a detailed explanation of prodrugs and methods to make them on page 17, line 21 through page 18, line 2 of the subject application. It is well-known by those skilled in the art and inherently described by our disclosure that a prodrug is a precursor of a drug, converted in its active form in the body by normal metabolic process. Just as the term "salt" or "solvate" is well understood by those of ordinary skill in the art no further definition of the term is required. Applicants note that the Examiner asserts that no guidance as how the compounds are made more active *in vivo*. Applicants do not understand the relevance of the Examiner's statement concerning the activity of prodrugs and its relationship to the enablement of prodrugs. There is no requirement in the patent statutes or case law requiring that a prodrug is only enable when it is more active *in vivo*. This makes no sense. The Examiner's position is unreasonable based upon that well developed and understood use of the term "prodrug" in the pharmaceutical industry.

Applicants again inform the Examiner that the term "prodrug" is common and standard language used commonly in patent applications and claims in the pharmaceutically arts. This is readily apparent if one performs a simple search for such terms in patents section of the USPTO website. More particularly, this fact is true if one performs a search of the patent literature for the term "prodrug" and the present Examiner and Supervisory Patent Examiner.

The present Examiner (and Supervisory Patent Examiner) of the instant application has issued patents containing the apparently rejected claim language on number of occasions in the recent past. Applicants have listed patents below with the claim language "prodrug" examined and issued by the Examiner Liu and Supervisory Patent Examiner Shah of the present application.

For example, U.S. Patent No. 6,486,185 ("the '185 patent"), issued on November 26, 2002, with the present Examiner and Supervisory Patent Examiner listed on the face of the patent includes in the claim language of claims the term "***prodrug***" *at least 12 times.* Applicants note that the patentee of the '185 patent provides a standard definition of a "prodrug" in the summary of the invention. No detailed explanation of how one makes prodrugs of the claimed compounds is provided. Applicants respectfully submit that the term "prodrug" is a well-known term of art and applicants are not required to provide a production specification in order to gain a patent. Furthermore, applicants note U.S. Patent No. 6,369,226 ("the '226 patent"), issued on April 9, 2002 with the present Examiner listed on the face of the patent includes in the claim term "***prodrug***" in each of the issued four claims. Again, the patentee provides a short standard definition of the term "prodrug" in the detailed description of the invention as "a compound that is converted under physiological conditions or by solvolysis or metabolically to a specified compound that is pharmaceutically active."

Applicants respectfully submit the use of the term "prodrug" is well-known and understood by those of ordinary skill in the art. Applicants have provided an enabling disclosure to those of ordinary skill in the art to make and use "prodrugs" of the compounds of the present invention. Furthermore, the present Examiner and Supervisory Patent Examiner has recognized this fact in the past as exemplified by the examples of claims issued by the present Examiner (and Supervisory Patent Examiner) of the instant application.

Applicants do not understand and would appreciate if the Examiner could articulate

how the use of the standard term "prodrug" in the present application is different from the numerous previous uses of the term in the patent literature and in the instant case apparently renders it non-enabled. The Examiner has not provided logical rationale for his position and how it comports with positions he has taken with the same term "prodrug" in the same art in the recent past. Accordingly, applicants respectfully request that the Examiner withdraw his rejection of claims 1 and 15 under 35 U.S.C. §112, first paragraph in view of the preceding remarks.

III. Rejections under 35 U.S.C. §112, Second Paragraph

On page 4 of the Action claims 1, 2, and 6 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner states that claims 27 and 28 are substantial duplicates of claims 13 and 14. The Examiner further states that use of the term "heterocyclic" and "heterocyclic" in claims 1-4, 15-18, 30-32 and 40-42 is unclear to the array of heteroatoms, ring size, as well as the nature of atoms as ring members. The Examiner further states that claim 49 is indefinite for allegedly indeterminate scope for the following reasons: (i) no particular disorder is recited: (ii) the claim language may read on disease not yet fully understood to be affected by receptor tyrosine kinase activity; and (iii) how does one determine who is "in need of such treatment" and who is not. Applicants respectfully traverse the Examiner's rejections of claims 1-4, 13-18, 27, 28, 30-32 and 40-42 under 35 U.S.C. §112, second paragraph and respectfully request that they be withdrawn in view of the following remarks.

Initially, applicants note that the Examiner on page 4, numbered paragraph 3 of the action states that claims 1, 2 and 6 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner concludes number paragraph 3 by stating that "[t]he following reasons apply:" and numbered paragraph 4 follows. However, paragraph 4 does not detail any reasons with respect to claim 6 but includes reasons for claims 3, 4, 13, 14, 27, 28, 15-18, 30-32 and 40-42. Applicants respectfully request clarification in the next action since the Examiner has failed to properly recited the 112 rejection in the November 22, 2002 Office Action.

The Examiner asserts that claims 27 and 28 are substantial duplicates of claims 13 and 14. Applicants respectfully submit that they have the right to restate their claimed invention in a reasonable number of ways. Claims 27 and 28 depend from claim 1, whereas claims 13 and 14 depend from a more limited independent claim 15. Nevertheless in order to advance prosecution of the subject application, without conceding the correctness of the Examiner's position, applicants have cancelled claims 27 and 28 of the subject application. Accordingly, applicants respectfully submit that the cancellation of claims 27 and 28 renders this rejection under 112 moot.

The Examiner's second section 112 rejection relates to the use of the term "heterocyclic" in claims 1-4, 15-18, 30-32 and 40-42. The Examiner alleges that the term "heterocyclic" is unclear to the array of heteroatoms, ring size, as well as the nature of atoms as ring members.

Applicants respectfully submit that the definition of the term "heterocyclic" is patently clear to one of ordinary skill in the art based upon applicants' disclosure, as well as the voluminous information on heterocyclics in the art. The definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure; (2) the teachings of the prior art; and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, for example, In re Marosi, 218 U.S.P.Q. 289 (Fed. Cir. 1983); Rosemount, Inc. v. Beckman Instruments, Inc., 221 U.S.P.Q. 1 (Fed. Cir. 1984); W.L. Gore & Assocs., Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (Fed. Cir. 1983).

Applicants provided on page 16, lines 15-36, a clear definition of heterocyclic. As defined by applicants a heterocyclic means an aromatic or non-aromatic heterocyclic group containing one to four heteroatoms each selected from O, S, and N, i.e., at least one heteroatom is present. Furthermore, applicants provided a long list of representative examples of heterocyclics on page 16 of the subject application.

The term "heterocyclic" is a well-known term used frequently by those of ordinary skill in the art. As such it is readily understandable to those of ordinary skill in the art. One skilled in the art readily recognizes that a heterocyclic as defined by applicants, and as known in the art, requires the presence of at least heteroatom in order to be considered a heterocyclic. Applicants respectfully submit that one of ordinary skill in the art reading the claims of the

subject application in view of the accompanying specification and the teachings of the prior art would understand what is claimed. Accordingly, applicants respectfully submit that they have provided an adequate and clear disclosure for the term "heterocyclic" and this disclosure coupled with the extensive teachings in the prior art, satisfies the requirements for the second paragraph of section 112.

Once again applicants respectfully submit that the term "heterocyclic" is not only well understood by those of ordinary skill in the art but also by the Examiner and Supervisory Patent Examiner of the present application. A simple search of the USPTO patent literature identifies patents with claims with the term "heterocyclic" issued by the Examiner and Supervisory Patent Examiner of the instant application. Applicants are at a loss for rationale behind the issuance of second paragraph 112 rejection over a term which is not only well understood and accepted by those of ordinary skill in the art but also well understood and part of the art recognized by the Examiners of the instant application.

Applicants direct the Examiners attention to the following U.S. patents which include claims with the apparently indefinite term "hereocyclic" issued by the Examiners of the instant application: 6,534,652 (term "heterocyclic" in claims with no definition of heterocyclic in the specification); 6,518,286 (term "heterocyclic" in claims with no definition of heterocyclic in the specification); and 6,469,014 (term "heterocyclic" in claims with no definition of heterocyclic in the specification). Applicants respectfully request the Examiner provide an explanation why he believes applicants use of the term "heterocyclic" is different from those in the patents he has issued in the recent past.

Applicants remind that Examiner unlike the aforementioned patents that they have provided a detailed explanation in the specification of the instant application with examples of the term "hetereocyclic". Applicants respectfully submit that the term "heterocyclic" is a term of art well-understood by those of ordinary skill in the art. Applicants are not required to provide the patent office with a production manual. Accordingly, applicants respectfully request that the Examiner withdraw his 112 second paragraph rejection of claims 1-4, 15-18, 30-32 and 40-42 in view of the preceding remarks.

With respect to the Examiner's 112 rejection, second paragraph of claim 49 applicants respectfully submit that that claim is directed to pharmaceutical composition for the treatment of hyperproliferative disorder in a mammal. Applicants again are at a loss for the reasons the

Examiner is rejection claim 49 under §112, second paragraph. The claim is a standard pharmaceutical composition of matter claim. Applicants are not required in a pharmaceutical composition of matter claim to recite a particular disorder. Applicants would appreciate if the Examiner could identify the patent statute or law, which requires a pharmaceutical composition to recite a particular disorder. Claim 49 is not a method of treatment claim rather it is a pharmaceutical composition of matter claim. The Examiner asserts that claim 49 reads upon disease not yet fully understood to be affected by a receptor tyrosine kinase antagonist. Applicants respectfully submit that the Examiner's point is irrelevant to the claim. Again applicants are not claiming a method of treatment, it is a pharmaceutical composition of matter claim. Lastly, the examiner recites the following language "in need of such treatment" which does not appear in claim 49 of the instant application. Applicants respectfully request the Examiner review claim 49 closely and more precisely inform applicants of the relevance of his statement. Applicants respectfully submit that the language used in claim 49 is standard pharmaceutical composition of matter claim language and additionally the specification provides details on page 30 on how one makes pharmaceutical compositions of the compounds of the present invention. Nothing further is required in order to practice pharmaceutical composition claim 49 of the present application. In view of the preceding remarks, applicants respectfully request that the Examiner withdraw his 112 second paragraph rejection of claim 49.

Rejection under 35 U.S.C. §103(a)

Claims 1-49 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over WO 1999/24440 (Munchhof et al.). The Examiner states that Munchhof et al. teaches a generic group of compounds that allegedly embrace many of applicants' claimed compounds. The Examiner directs applicants' attention to formula I, page 2, wherein X^1 can be CH, R^2 is 5-13 membered heterocyclic, R^{11} can be $-C(O)NR^6R^9$, $-C(O)(C_6\text{-}C_{10}$ aryl), etc. The Examiner states that compounds of Munchhof et al. are useful for the treatment of hyperproliferative disorders. The Examiner further states that the claims of the instant application differ from Munchhof et al. by allegedly reciting species and/or genus that are more limited than the genus found in Munchhof et al. Applicants respectfully traverse the

rejection of claims 1-49 under 35 U.S.C. §103(a) and respectfully request that the Examiner reconsider the rejection in view of the following remarks.

The Examiner asserts in his rejection that the claims of the subject application differ from the reference by reciting species that are more limited than the genus found in Munchhof et al. Applicants take issue with this assertion. Muchhoff et al. disclosure does not embrace applicants claimed invention. Applicants claim thiophenes wherein the substituent R^{11} of formula 1 is defined as follows:

> R^{11} is $-C(O)NR^{12}R^{13}$, $-(CH_2)_tNR^{12}R^{13}$, $-NR^{12}C(=O)R^{13}$, $-SO_2R^{12}$, $-SO_2NR^{12}R^{13}$, $-NR^9SO_2R^{12}$, $-NR^9SO_2NR^{12}R^{13}$, $-C(=N\text{-}OR^{12})R^{13}$, $-C(=NR^{12})R^{13}$, $-NR^9C(=NR^{12})R^{13}$, $-C(=NR^{12})NR^9R^{13}$, $-NR^9C(=NR^{12})NR^9R^{13}$, $-C(O)R^{12}$ and $-CO_2R^{12}$ and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_6 alkyl, $-(CH_2)_t(C_3$-C_{10} cycloalkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6 and q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of the foregoing R^{12} and R^{13} groups are optionally substituted by 1 to 3 substituents independently selected from R^5 or R^{12} and R^{13} taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are optionally substituted by 1 to 5 R^5 substituents, with the proviso R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

In contrast in Munchhof et al. defines the equivalent substituent as follows:

> R^{11} is H, C_1-C_6 alkyl, -C(O)NR^6R^9, -C(O)(C_6-C_{10} aryl), -$(CH_2)_t$(C_6-C_{10} aryl), or -$(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer ranging from 0 to 6, wherein said R^{11} groups, other than H, are optionally substituted by 1 to 5 R^5 groups;

Apparently the Examiner is able to divine a species/genus relationship between the instant application and Munchhof et al. notwithstanding the completely different definitions of the substituent R^{11} shown above. Thus, the premise upon which the Examiner is applying Munchhof et al. to the claims of the present invention is incorrect. Munchhof et al. cannot encompass applicants' claimed invention since applicants definition of at least the substituent R^{11} is completely different from that of Munchhof et al.

Applicants respectfully submit that the Examiner has not shown where the motivation to establish a *prima facie* case of obviousness is found in Munchhof et al. The Examiner asserts that one of ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds have been suggested by the reference as a whole. Applicants' respectfully submit that such a motivation does not exist *except* in the presence of applicants' disclosure. Applicants submit that the Examiner has divined the claimed invention *not* by looking at the disclosure of Munchhof et al. It is improper for the Examiner to use applicants' disclosure as the road map for the claimed invention and thus the source of the *necessary* motivation to find the claimed invention obvious. In the absence of applicants' disclosure no motivation exists. Applicants' disclosure is not part of the prior art. The Examiner is using a classic hindsight construction to arrive at the claimed invention. This is improper.

Applicants submit that even if one assumes for the sake of argument there is a genus-species relationship between Munchhof et al. and the claimed invention, the Examiner failed to satisfy the motivation requirement for a *prima facie* case of obviousness. Some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g. In re Deul, 34 U.S.P.Q.2d 1210, 1215 (Fed. Cir. 1995).

The Examiner has failed to support his assertion that Munchhof et al. motivates one of ordinary skill in the art to make the claimed invention. Where is the motivation the Examiner is referring to in Munchhof et al.? How would one arrive at the claimed invention based upon Munchhof et al., in the absence of the claimed invention? What particular teaching(s) directs those of ordinary skill in the art to make the claimed invention? Munchhof et al. discloses a genus of compounds that provides for a myriad of possible compounds to be made.

Applicants respectfully submit that it is improper for the Examiner to pick and choice elements from Munchhof et al. with *no* apparent reason for such choices. It is well establihed that the necessary motivation must be present in the art. The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications to arrive at the claimed compound. In re Lalu, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Arriving at the claimed invention in the absence of the necessary motivation cannot be used to establish a *prima facie* case of obviousness.

The Federal Circuit in Dillon, 16 U.S.P.Q.2d 1897, 1901 (1990) stated that explicit findings on motivation or suggestion to select the claimed invention should be articulated in order to support a 35 U.S.C. §103 ground of rejection. Applicants respectfully submit that the Examiner has failed to articulate rationale or facts that would support his underlying conclusion that the disclosure of Munchhof et al. renders obvious the claimed invention. The Examiner has merely selected portions of Munchhof et al. which allegedly overlap with applicants' claimed invention. The Examiner provided no particular reason(s) or rationale for selecting each of the elements identified or for that matter why one would combine them in the manner suggested by the Examiner.

Where is the teaching in Munchhof et al. pointing one of ordinary skill the art to pick the elements identified by the Examiner? The Examiner appears to be looking to find elements from Munchhof et al. that allegedly overlap with the claimed invention, without any reason for their particular selection. This is an improper. The Examiner has not stepped into the shoes of one of ordinary skill in the art at the time of the invention. Rather he has stepped into the shoes with the knowledge gleaned from applicants' disclosure. Applicants respectfully submit that a finding of obviousness based on such a practice is not proper and cannot render the claimed invention obvious.

The fact findings should specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus. In re Kulling, 14 U.S.P.Q.2d 1056, 1058 (Fed. Cir. 1990); Panduit Corp. v. Dennison Mfg. Co., 1 U.S.P.Q.2d 1593, 1606 n.42 (Fed. Cir. 1987). The Examiner has failed to show where the motivation to pick applicants' alleged subgenus from Munchhof et al's disclosure. As has been noted, applicants disagree with the assertion that their genus is a subgenus of those in Munchhof et al. Applicants respectively submit that the motivation to make an invention must be provided by the prior art applied against it, not from the disclosure of the claimed invention.

The Examiner has failed to meet his burden of specifically articulating where Munchhof et al. teaches or suggests that one of ordinary skill in the art would have been motivated to make the claimed invention. Without such a fact finding the Examiner cannot maintain an obviousness rejection for the claimed invention. Accordingly, applicants respectfully request that the Examiner withdraw his rejection of claims 1-49 under 35 U.S.C. §103(a) over Munchhof et al.

Conclusion

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for rejection set forth in the November 22, 2003 Office Action and earnestly solicit allowance of the claims pending in the subject application.

Respectfully submitted,

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